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The bi-directional communication and interaction between the brain and the immune system is one of the most exciting areas of biomedical research. Although many symposia contain sessions relating to the above topic (e.g. Experimental Biology '94, Neurosciences), there are few meetings devoted exclusively to this topic. Most of these have been in foreign countries, which limits the participation of American scientists. Some 25 distinguished scientists lectured in the workshop/symposium, and another 50-60 scientists were participants. The symposium was held in a state-of-the-art conference facility, and there was ample opportunities for one-on-one discussion of science. A more detailed description of the symposium is provided below.

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21 November 1994

Dr Matthew J Kluger,
Director, Institute for Basic and Applied Medical Research
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2425 Ridgecrest Drive SE
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USA

Dear Dr Kluger

Re: **Manuscript No. 1075, "Symposium Report - Neuroimmunomodulation: Stress and Immune Function."**

Thank you very much for your most interesting and stimulating review and enclosed Abstracts of the Meeting written with Michael Powanda on the above Conference. I have much pleasure in accepting this for publication in the Journal.

By way of a small token thanks. I am arranging with the publisher for you to receive one year's subscription of the Journal gratis.

I have passed on the manuscript for the preparation of proofs and you should receive these shortly from the publisher.

Once again very many thanks for your effort in submitting such a timely and interesting review.

With kind regards.

Yours sincerely

K D Rainsford, PhD. FRCPath, FRSC, FIBiol
Editor

cc Dr M C Powanda, M/P Biomedical Consultants, Mill Valley, California, 94941, USA.

Conference Perspective
Neuroimmunomodulation: Stress and Immune Function
The Lovelace Institutes, Albuquerque, New Mexico
7-9 October 1994

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At this meeting, as at a number of recent meetings wherein the latest cellular and molecular techniques have been used to revisit and reevaluate long standing biological questions and observations, the past has indeed become prologue. In many cases, as with sections of this meeting, the questions or observations are 25 to 30 years old, such as the seminal studies by Dr. William R. Beisel and his colleagues at the U.S. Army Medical Research Institute of Infectious Diseases. This series of studies documented the relatively constant constellation of metabolic, physiologic and endocrinologic changes which occur during bacterial, viral and rickettsial diseases in humans and other species. The wisdom of the ancient Greeks also was demonstrated at this conference: the virtues of a sound mind in a sound body.

The meeting began with Dr. Seymour Reichlin (New England Medical Center and Vail, Arizona) listing both the clinical conditions and preclinical data that attest to the presence and consequences of neuroendocrine-cytokine interactions. As some of the consequences of such interactions he cited: pituitary-adrenal activation; inappropriate ADH secretion; sick euthyroid syndrome; sick hypogonadal syndrome; sick bone syndrome; impaired insulin secretion and insulin resistance; and sick brain syndrome, also known as sickness behavior. In every case there is growing evidence of endocrine-cytokine interactions. Moreover, these interactions between cytokines and neurohormones may elicit adverse neurologic side effects when cytokines are given therapeutically. For example, in a 1987 study of 44 patients given IL-2 and lymphokine activated killer cells, 5 patients developed moderate cognitive impairment, 22 displayed delirium and severe cognitive impairment, while 7 exhibited delusions, escape behavior and picking at their bedclothes (the last a condition which Dr. Reichlin noted was described by Galen and is often found in the severely ill). Interferon $\alpha 2$ treatment of hepatitis C also is generally accompanied by fever, chills and fatigue, but in 17% of cases evokes serious brain dysfunction to include suicidal tendencies.

Dr. Rodney Langman (Salk Institute for Biological Studies) argued that the immune system "hijacked" existing effector functions to create a scheme whereby the host can distinguish between self and non self. He suggests that the immune system is unique to vertebrates while "immune responses" can be found even in single cell creatures. Dr. Langman made an impassioned plea to begin collecting the data on cytokine and neuroendocrine effects and interactions in a central location so the information can be processed and integrated into a "consensus model of neuroendocrineimmunology." He volunteered to be the contact person to begin collecting data on the ligands, the receptors and the cell types, as well as on the biological actions of, and physiologic responses, to hormones and cytokines. Some in the audience thought that this would be an insurmountable task unlikely to yield much information about a complex system, however as meta-analysis has shown, computer systems can often find patterns in multiple sets of data that may not be apparent from individual studies.

Dr. Edward Bernton (Walter Reed Army Medical Center, Washington, DC) reminded the audience that despite the bloody nature of battle, it was infections not injuries that have caused more casualties in war, even as recently as the Korean, Vietnam and Gulf wars. In addition to being hazardous, war and the training for war is stressful. To assess the effects of such stresses on the endocrine-immune system(s) 300 Ranger trainees were studied over a period of 8 weeks during the desert, mountain, forest and swamp phases of their training. On average these healthy individuals lost 9-10% of their body weight, virtually all as fat, had 3-4 hours of sleep per day, operated at high level of activity, and were subjected to a wide variety of stresses as might occur in battle. By the end of the 4th week, at the completion of the mountain phase of training which was the most strenuous phase, serum cortisol levels increased while that of testosterone and IGF-1 decreased. At this time, the skin test to an array of antigens was 40% of normal while 20% of the trainees were anergic. The skin test response correlated with testosterone levels. While T cell function was decreased, IgE levels increased. White cell secretion of IL-1α, IL-6 and TNF in response to endotoxin was decreased. Attempts to eliminate these alterations in the neuro-immune responses by increasing food intake yielded equivocal results.

While exhausting exercise coupled with sleep deprivation and a variety of additional stresses clearly is immunosuppressive, according to Dr. Laurie Hoffman-Goetz (University of Waterloo, Ontario, Canada) acute maximal exercise by itself appears to increase the number of natural killer (NK) cells and increase NK and lymphokine activated killer (LAK) cell activities. Whether these increases in natural immune functions have benefit to the host may depend upon the nature of the disease, for example, the dissemination of mammary adenocarcinoma tumors appears unaffected by NK or LAK cell activity.

In regard to stress, it appears to make no difference whether one is man or mouse. Dr. John Sheridan (Ohio State University) showed that restraint stress increased

plasma corticosterone levels and tissue responses to norepinephrine, but reduced the cellular immune responses of C57 black 6 mice to respiratory influenza A infection. The elevated plasma corticosterone levels correlated with reduced lymphocyte trafficking to the lungs and to the draining lymph nodes of the infected mice. While cell accumulation at the inflammatory site and lymphadenopathy were restored by treating the animals with a glucocorticoid receptor antagonist, restoration of T cell activation only occurred when a β-adrenergic receptor antagonist was given, suggesting a role for catecholamine in the regulation of T cell activation.

According to Dr. Bruce McEwen (Rockefeller University), glucocorticoids can modulate immune cell trafficking as a function of the glucocorticoid receptors on such cells, as well as of tissue factors such as corticosteroid binding globulin and steroid catabolizing enzymes. Diurnal and stress-induced increases in glucocorticoid elicit increases in neutrophil and eosinophil count and decreases in B and T cells. The decrease in B cells appears to be totally glucocorticoid dependent, whereas the effects on other immune cells appear to involve factors in addition to glucocorticoid.

Given that neuro endocrine-cytokine interactions exist, one might expect that cytokines would need to cross the blood-brain barrier to have an effect. Dr. William Banks (Veterans Affairs Medical Center, New Orleans) demonstrated that IL-1 does cross the blood-brain barrier by means of a saturable transport system and that IL-1 receptor antagonist (IL-1ra) inhibits transport of IL-1α at 50 to 60 fold lower concentrations of IL-1ra than is needed to produce an equivalent inhibition of IL-1β transport. The physiologic and immunologic consequences of this selective inhibition are as yet unknown, but these data should be kept in mind if IL-1ra is used to treat acute or chronic inflammation.

Evidence that minute (femtomolar) amounts of IL-1β injected into the brain are sufficient to suppress a variety of peripheral immune cell responses was provided by Dr. Jay Weiss (Emory University, Atlanta, GA). CNS IL-1 suppression of peripheral immune responses requires corticotrophin releasing factor (CRF) as an intermediate in that antiserum to CRF blocked the IL-1 induced immunosuppression. In addition, Dr. Weiss has recently found that the HIV envelope protein gp120 injected into rat brain causes a release of IL-1 and suppression of peripheral cellular immune responses. Dr. Jean Merrill (University of California Los Angeles) showed that a full length HIV envelope protein containing gp120 and gp41 induced the production of both IL-1 and TNFα in rodent glial cell cultures. Detailed analysis of selected protein fragments showed that IL-1 and TNFα were induced by different epitopes.

Diminished intellectual function and motor impairment also is common in people with AIDS. Dr. Anna da Cunha (National Institute of Mental Health, NIH, Bethesda, MD), found that there is an increase in the mRNA encoding the peptide neurotransmitter preprosomatostatin (SRIF) in layer IV of the frontal cortex in

HIV-seropositive children and SIV-infected juvenile rhesus macaques with cognitive impairment. IL-1 is known to induce SRIF, but whether IL-1 or other cytokines are actually responsible for both the cognitive and motor dysfunction of AIDS dementia can not be determined from neuro-anatomical studies alone.

Dr. Robert Dantzer (INSERM, Bordeaux, France) provided evidence for a scheme by which cytokines released peripherally can induce the centrally (CNS) mediated sickness behavior described by Dr. Reichlin. This scheme involves activation of primary nerve endings by a prostaglandin-dependent mechanism; conduction of this signal via the vagus nerve (cutting the vagus nerve blocks the sickness behavioral effects of peripherally administered IL-1); induction of cytokine gene expression in the brain; the action of these CNS produced cytokines on neurons and/or glial cells (centrally administered IL-1ra blocks the behavioral effects of peripherally administered IL-1); and the induction by these CNS cytokines of hormones (e.g., glucocorticoids) and neuropeptides (e.g., vasopressin) which act to moderate the behavioral effects of the cytokines.

One particular aspect of sickness behavior is disruption of sleep patterns, generally characterized by an initial period of enhanced slow-wave sleep (SWS) followed by a period of reduced sleep. Dr. James Krueger (Univ. Tennessee, Memphis, TN) described what is known about cytokines and the regulation of sleep. Interleukin-1 (IL-1) α and β, tumor necrosis factor (TNF) α and β, interferon-α, and acidic fibroblast growth factor all enhance sleep whether given intravenously or intracerebroventricularly. The effect of these cytokines appears not to be limited to illness associated sleep changes. Antibodies to IL-1β or to TNFα, as well as a soluble TNF receptor and IL-1RA reduce normal sleep. The mechanisms by which cytokines elicit sleep do not appear to involve prostaglandins, opioids or insulin, but may be mediated by growth hormone releasing hormone (GHRH). Growth hormone release is linked to SWS and GHRH is somnogenic in rats, rabbits and man. Antibodies to GHRH block IL-1-induced growth hormone release and IL-1-induced sleep responses. Nitric oxide (NO) is also somehow involved; GHRH and IL-1 enhance NO production, while inhibition of NO production blocks IL-1-induced sleep.

Another aspect of sickness behavior is fever. Dr. Matthew Kluger (The Lovelace Institutes, Albuquerque, NM) presented evidence that IL-1β acts in the anterior hypothalamus to produce fever and that IL-6 appears to be involved. Intrahypothalamic injection of neutralizing antibody to IL-1β attenuates fever and suppresses the rise in hypothalamic IL-6. According to Dr. Bryan Spangelo (University of Nevada, Las Vegas), IL-1β also induces IL-6 release in the anterior pituitary via lysophosphatidylcholine activation of protein kinase C. IL-6 stimulates the release of prolactin, growth hormone and luteinizing hormone from male rat anterior pituitary cells in vitro. Antibody to IL-6 reduced, but did not eliminate prolactin release.

Dr. Kluger also showed that physiological levels of corticosterone increased TNF and IL-6 release from isolated perfused rat livers. Epinephrine via a β-mediated pathway also led to an increase in IL-6 secretion from liver. It appears that these stress hormones exhibit a degree of duality: they can increase the circulating levels of some cytokines as well as can moderate the effects of these self same cytokines.

According to Dr. Adrian Dunn (Louisiana State University Medical Center, Shreveport, LA) many of the behavioral responses associated with sickness while initiated by cytokines such as IL-1 are mediated by corticotrophin-releasing factor (CRF). Intracerebroventricular (icv) injections of CRF elicit sickness behavior and icv injections of a CRF antagonist block these behavioral responses.

It appears that not only are many forms of stress immunosuppressive, but so too are substances we often use when under stress - tobacco and alcohol. Dr. Mohan Sopori (The Lovelace Institutes, Albuquerque, NM) showed in both *in vivo* and *in vitro* studies that nicotine activates lymphocytes making them refractory to subsequent antigen-mediated activation. The effect of nicotine may be related to the presence of nicotine acetylcholine receptors on lymphocytes. Chronic alcohol consumption also is immunosuppressive; this effect of alcohol appears to be a dominant genetic trait. Chronic ethanol ingestion suppresses the antibody plaque-forming cell response in LEW rats and LEW x F344 progeny, but not in F344 rats.

Dr. J. Edwin Blalock (University of Alabama, Birmingham, AL) suggested that the immune system acts as a sensory organ for non-cognitive stimuli, such as bacteria, viruses and tumors. He indicated that the neuroendocrine and the immune systems share many of the same ligands and receptors. For example, lymphocytes have been shown to produce ACTH, prolactin, TSH, endorphins and growth hormone; in fact growth hormone appears to act as autocrine regulator in lymphocytes. Conversely, the pituitary has a receptor for IL-1 and IL-1 can act directly to induce CRF which stimulates ACTH release. CRF also sensitizes the pituitary so that subsequent exposure to IL-1 causes a persistent ACTH release. Such sensitization might allow a series of mild inflammatory stresses to produce a disproportionate glucocorticoid response. Dr. Blalock also briefly discussed a pituitary-derived factor called "suppressin" which appears to block the blastogenic response and, in preliminary studies, to inhibit lymphoid tumor growth.

Evidence for a role of the sympathetic nervous system in modulating immune system responses was provided by Dr. Suzanne Felten (University of Rochester School of Medicine). Treatment of adult mice with 6-hydroxydopamine (6-OHDA) depletes peripheral organs, including lymphoid organs, but not the CNS, of 90-95% of norepinephrine content by 24 hours. This chemical sympathectomy increases background proliferation in inguinal and axillary lymph nodes, spleen and bone marrow in non-immune mice. Upon stimulation lymph node T cell response was reduced and B cell response increased, but with a reduction in IgM and an increase

in IgG. Splenic B cell responses differed from that of lymph nodes; LPS-induced proliferation was decreased with no changes in IgM or IgG concentrations.

Much of the focus of stress research in general and this meeting has been on the factors of neuro, endocrine or cytokine origin which propagate stress. As an antidote, Dr. James Lipton (Univ. Texas SW Med Ctr at Dallas), discussed α-MSH which appears to be following IL-1 into the pantheon of virtually ubiquitous endogenous mediators, which may be appropriate considering the range of its potent antiinflammatory activities. α-MSH is found in many areas through out the brain and body, with large amounts found in the skin and gut. α-MSH has been shown to moderate acute inflammation induced by irritants and cytokines; the delayed hypersensitivity reaction; chronic inflammation (Mycobacterium arthritis); and systemic inflammation associated with endotoxemia, sepsis, peritonitis and adult respiratory distress (ARDS). In a cecal ligation model of peritonitis which is uniformly fatal, α-MSH increases survival to 40% and acts additively with gentamicin to attain 70% survival. In ARDS, α-MSH inhibits neutrophil migration and accumulation of neutrophils in the bronchi. α-MSH may exert its antiinflammatory actions by it ability to inhibit nitric oxide production by macrophages. Dr. Lipton proposed an interesting inflammo-modulatory cycle based on the fact that macrophages both produce and have receptors for α-MSH while neutrophils appear to have only receptors for α-MSH, thus, in macrophages α -MSH could act as an autocrine. Since macrophages succeed neutrophils at wound sites one wonders if this difference between macrophages and neutrophils allows for a non-specific inflammatory response, which could be destructive if unchecked, to be converted into a controlled healing response.

If cytokines are active in the CNS, one might expect that repeated or chronic administration of pro-inflammatory cytokines might induce CNS dysfunction or disease. Dr. Iain Campbell (The Scripps Research Institute, La Jolla, CA) described the effects of chronic expression of cytokines in the CNS of transgenic animals. A GFAP expression vector was used to target astrocytes in the CNS for the expression of IL-6, IL-3 or IFN-α. Cerebral expression of each of these cytokines at high levels led to an early death. Expression at low levels was associated with a progressive neuropathy, but allowed time for development of breeding lines. All cytokines caused neurodegeneration and astrocytosis. IL-6 alone caused demyelination, angiogenesis, diffuse blood-brain barrier leakage and upregulation of acute-phase protein synthesis as well as increased deposition of these proteins. IL-3 alone caused menigoencephalitis; both IL-3 and IL-6 caused perivascular cuffing and microgliosis. IFN alone caused induction of MHC class I and 2,5-oligoadenylate synthase gene expression. Whether or not such transgenic animals can be developed into models for a variety of neurodegenerative diseases remains to be determined, but it is clear that chronic expression of cytokines in the CNS produces many of the changes associated with such diseases.

Neurocytokine interactions appear to occur even in the womb. Evidence that cytokines might play a role in brain function and perhaps in brain development at the fetal stage was adduced by Dr. G. Miller Jonakait (Rutgers University, Newark, NJ). Murine interferon-γ (IFN-γ) markedly increases choline acetyltransferase (ChAT) activity in cultured rat embryonic septal nuclei with adjacent basal forebrain. The data indicate that IFN-γ increases the amount of mRNA coding for ChAT and suggests that IFN-γ encourages the differentiation of cholinergic neurons from undifferentiated precursors. A microglial-derived intermediate appears to be involved.

In the event there remained any doubt that a powerful link exists between brain function and immune function, Dr. Nicholas Cohen's (University of Rochester Medical Center, Rochester, NY) presentation of the effects of a gustatory conditioned stimulus on antibody production provided food for thought. In short, after conditioning a booster dose of antigen which by itself was unable to elicit a significant antibody response was found to be as effective as a 100 fold greater dose of antigen. Could these data indicate that the potency of drugs and vaccines might be enhanced by carefully chosen psychological stimuli? Could the mechanism of the placebo effect be so explained?

The meeting closed with a masterful summary by Dr. David Felten (Univ. Rochester Med Ctr) who listed a series of key themes that emerged during the meeting. One theme involved the accumulation of evidence that there were functional receptors for hormones and neurotransmitters on tissues and cells of the immune system, the thymus, the spleen, T and B lymphocytes and macrophages. A second theme had to do with the growing evidence that neurohormones are produced and are active in the immune system and conversely that cytokines are produced and active in what has classically been considered the neuroendocrine system. It should be emphasized that though there are many instance of neuro-immune interactions, not every stimulus that generates an immune response also elicits a neuroendocrine response. For example, while LPS stimulates both immune and neuroendocrine responses, KLH evokes only an antibody response without any glucocorticoid response.

The third theme emphasized that there were a wide range of cytokine interactions with the nervous system and conversely, there is a diversity of neurotransmitter interactions with primary (thymus and bone marrow) and secondary (spleen, lymph nodes) lymphoid tissues, as well as with target organs such as liver. It has long been known that neurotransmitters interact with one another to produce synergistic or antagonistic effects and a parallel situation has been observed to exist among the cytokines. But only recently has it become clear the these two systems crosstalk extensively. While this crosstalk probably works to the advantage of the host during sickness, following injury, and in health, it does not make the elucidation and/or manipulation of these interactions easier for the preclinical and clinical investigators.

Dr. Felten ended by reminding the audience that most of the studies reported at this meeting were done in young, healthy animals or humans subjected to an acute or limited duration physiologic or inflammatory stress or induced disease. These studies leave unanswered the effects of a chronic stress or disease and the alterations and adaptations associated with aging. An additional factor which was not discussed was the perception and effect of pain on neuro-immune interactions. Amelioration of pain has been shown to facilitate healing after surgery.

Concluding Comments

As this conference amply demonstrated, molecular biology provides the tools to examine in exquisite detail the individual components of complex biological systems. However, molecular biology in and of itself gives little or no insight as to how these components are arrayed and interact to form a functional system. It is only by the concomitant study of molecular, cellular, intercellular (local), tissue, organ and organism (systemic) changes that a clinically relevant corpus of information will be derived. The present and foreseeable scarcity of research funds relative to the plethora of proposed projects suggests that more such integrative studies should be designed to most fruitfully use the funds that are available. Meetings such as this, in which multiple facets, systemic as well as local, of neuroimmune interactions in sickness and in health were discussed, gives some indication as to the value of this approach.